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(54) Title: METHOD AND COMPOSITIONS FOR IDENTIFYING ANTI-HIV THERAPEUTIC COMPOUNDS

(57) Abstract: The invention relates to methods and compositions for identifying compounds having therapeutic activity against human immunodeficiency virus (HIV).

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP 03/12423

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07F9/40 C07F9/6561 G01N33/04

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07F C07H C12N C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HAMMOND, J. L. ET AL.: "Alkylglycerol Prodrugs of Phosphonoformate..." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 45, no. 6, June 2001 (2001-06), pages 1621-1628, XP002277443 page 1622; figure 1	1,7, 14-17, 19,20, 27,38, 42,43,62
X	HAKIMELAHI G H ET AL: "DESIGN, SYNTHESIS, AND STRUCTURE-ACTIVITY RELATIONSHIP OF NOVEL DINUCLEOTIDE ANALOGS AS AGENTS AGAINST HERPES AND HUMAN IMMUNODEFICIENCY VIRUSES" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 38, no. 23, 1995, pages 4648-4659, XP001145914 ISSN: 0022-2623 page 4648 - page 4652; table 4	1,7,8, 10, 12-15, 20,27, 38,39, 41,43, 62,67
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

\* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/12423

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	KRAUS J-L: "NEW PHOSPHONATE ANALOGUES OF 3'-THIA-2',3'-DIDEOXYCYTIDINE (BCH-189) SYNTHESIS AND ANTI-HIV EVALUATION" NUCLEOSIDES & NUCLEOTIDES, DEKKER, NEW YORK, NY., US, vol. 12, no. 2, 1993, pages 157-162, XP009004946 ISSN: 0732-8311 scheme 1 page 157, line 22 - page 158	1,7,20, 27,38
X	CHARVET ET AL: "Inhibition of Human Immunodeficiency Virus Type 1 Replication by Phosphonoformate- and Phosphonoacetate- 2',3'-Dideoxy-3'-thiacytidine Conjugates" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 14, no. 37, 1994, pages 2216-2223, XP002072425 ISSN: 0022-2623 schemes 1-3: compounds 3,4,5-10, 12,13, 17,18; "Biological Results" table 1 page 2219, column 2, paragraph 2	1,7,20, 38-40, 42,43,62
X	MENENDEZ-ARIAS L: "Targeting HIV: antiretroviral therapy and development of drug resistance" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 23, no. 8, 1 August 2002 (2002-08-01), pages 381-388, XP004386181 ISSN: 0165-6147 figure 1	17,64,65
X	WO 01/39724 A (UNIV CALIFORNIA SAN DIEGO ; KINI GANESH D (US); BEADLE JAMES R (US); H) 7 June 2001 (2001-06-07) page 3, line 4 - page 16, line 20; claims 1-6,13-15	1,7,8, 10, 12-15, 20,27, 38,39, 41,43, 62,67
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/12423

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BALLATORE, C. ET AL.: "Synthesis and Evaluation of Novel Amide Prodrugs of PMEA and PMPA" BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, vol. 11, no. 8, 23 April 2001 (2001-04-23), pages 1053-1056, XP0001180825 page 1054, column 2 - page 1055, column 2; figures 1,3,4; table 1	1,7,8, 10,12, 13,20, 27,38, 41,43, 62,67
X	WO 01/96354 A (MARLIERE PHILIPPE ; POCHET SYLVIE (FR); CENTRE NAT RECH SCIENT (FR); P) 20 December 2001 (2001-12-20) page 1, line 26 - page 7, line 11; claims 26,27	1,7,15, 16
X	page 11, line 26 - page 12, line 4	17,20,27
X	page 12, line 5 - line 8; claims 21,28	38,40,43
A	CLERCQ DE E: "NEW DEVELOPMENTS IN ANTI-HIV CHEMOTHERAPY" CURRENT MEDICINAL CHEMISTRY, BENTHAM SCIENCE PUBLISHERS BV, BE, vol. 8, no. 13, November 2001 (2001-11), pages 1543-1572, XP009012547 ISSN: 0929-8673 the whole document	1
X	WO 02/08241 A (GILEAD SCIENCES INC ; BECKER MARK W (US); HE GONG XIN (US); LEE WILLIA) 31 January 2002 (2002-01-31)	1,7, 12-15, 17,20, 27, 38-41, 62, 67-70, 73,74, 76,78, 82,86
X	page 2 - page 16; claim 4; examples 1a,1b,2-7,9; table 7	71
X	page 11; claims 1,4-6,8	72
X	page 10, line 20 - line 24	
X	GORIN B I ET AL: "A Novel Esterification Procedure Applied to Synthesis of Biologically Active Esters of Foscarnet" TETRAHEDRON LETTERS, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 38, no. 16, 21 April 1997 (1997-04-21), pages 2791-2794, XP004058495 ISSN: 0040-4039 Scheme 1 page 2792; compound 1	38
A	page 2793	43

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/12423

C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/103008 A (GOUILAEV ALEX HAAHR ; NOERREGAARD-MADSEN MADS (DK); SLOEK FRANK ABILGA) 27 December 2002 (2002-12-27) pages 104, 266, 316, page 308 – page 309; examples 4, 15, 25, 26, 31, 32 page 13, paragraph 1	38-41
X	DATABASE MEDLINE 'Online! US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; May 2002 (2002-05), POKROVSKII A G ET AL: "Comparative analysis of HIV-1 resistance to AZT and AZT H-phosphonate in a cell culture." XP002296489 Database accession no. NLM12134511 abstract & DOKLADY. BIOCHEMISTRY AND BIOPHYSICS. 2002 MAY-JUN, vol. 384, May 2002 (2002-05), pages 152-154, ISSN: 1607-6729 & DOKLADY AKADEMII NAUK, vol. 384, no. 2, May 2002 (2002-05), pages 259-262, ISSN: 0869-5652	43 1, 18
A	DE CLERCQ E: "Chemotherapy of human immunodeficiency virus (HIV) infection: anti-HIV agents targeted at early stages in the virus replicative cycle" BIOMEDICINE AND PHARMACOTHERAPY, vol. 50, no. 5, 1996, pages 207-215, XP002296486 ISSN: 0753-3322 figure 13	2, 5-7
T	US 2004/121316 A1 (CHEN XIAOWU ET AL) 24 June 2004 (2004-06-24)	1, 23, 24, 38-44, 46-61
	abstract	
X	SAUBER K ET AL: "A new esterase for the cleavage of pivalic acid-containing prodrug esters of cephalosporins." ENZYME AND MICROBIAL TECHNOLOGY. JUL 1996, vol. 19, no. 1, July 1996 (1996-07), pages 15-19, XP002296487 ISSN: 0141-0229 page 15, column 1 – page 17, column 2; table 1	71

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## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/12423

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MENDES EDUARDA ET AL: "Synthesis, stability and in vitro dermal evaluation of aminocarbonyloxymethyl esters as prodrugs of carboxylic acid agents." BIOORGANIC & MEDICINAL CHEMISTRY. MAR 2002, vol. 10, no. 3, March 2002 (2002-03), pages 809-816, XP002296488 ISSN: 0968-0896 page 810 - page 815	71

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/12423

### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 21, 22, 28, 29, 30, 45, 196-213, partially 1, 8, 13-17, 20, 23, 27 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 8,13-17,20,27;69 partly: 1,7,10,12,38-44,62-68,70

Methods for identifying a compound and determining the anti-HIV activity of its phosphonate derivative. Means for the method.

2. claims: 3; partly: 1,19, 38-44

Methods for identifying a compound and determining the anti-HIV activity and tissue selectivity of its phosphonate derivative or metabolite. Means for the method.

3. claims: 4; partly: 1,19, 38-44

Methods for identifying a compound and determining the anti-HIV activity and intercellular residence time of its phosphonate derivative or metabolite. Means for the method.

4. claims: 6,36; partly: 2,5,7,10,11,12,25,26,31-34

Methods comprising selecting a non-nucleotide compound containing at least one esterified carboxyl group and determining the intracellular persistence of the compound or a esterolytic metabolite of the esterified carboxyl thereof

5. claims: 35,37; partly: 2,5,7,9 -12,25,26,31-34

Methods comprising selecting a non-nucleotide compound containing at least one esterified phosphonate group and determining the intracellular persistence of the compound or a esterolytic metabolite of the esterified phosphonate thereof

6. claims: 18; partly: 1, 38-44

Methods for identifying a compound and determining the anti-HIV activity and the resistance of HIV to the phosphonate derivative of the compound or metabolite thereof. Means for the method.

7. claims: 46-61; partly: 1,23,24,38, 40-44

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Methods for identifying a compound and determining the anti-HIV activity and susceptibility to hydrolysis of its carboxyl esters by GS-7340 Ester Hydrolase. Means for the method.

8. claims: partly: 38-44, 62-68, 70

Method for identifying an anti-HIV compound and substituting it with an esterified carboxylate and assaying the product for its anti-HIV activity.

9. claims: 208, 242, 246; partly: 71-72, 210, 214, 218, 222, 234, 238-241, 243, 244, 247-250

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract capable of catalysing the hydrolysis of a carboxylic ester.

10. claims: 245, 196; partly: 71-72, 210, 214, 218, 222, 234, 238-241, 243, 244, 247-250

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified carboxylate group and contacting the compound with an extract capable of catalysing the hydrolysis of a carboxylic ester.

11. claims: Partly 73-75, 77-102

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract of peripheral blood having carboxylic ester hydrolase activity to produce a metabolite compound

12. claims: 76, 200, 204; Partly 73-75, 77-102

Prodrugs and method for identifying prodrugs involving the provision of a compound having an esterified carboxylate group and contacting the compound with an extract of peripheral blood having carboxylic ester hydrolase activity to produce a metabolite compound.

76, 200, 204

Partly 73-75, 77-102,

13. claims: 103-134, 198, 201, 205, 206, 209, 211, 212, 215, 216, 219, 220, 223, 224, 235, 236

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Prodrugs and method for identifying prodrugs having an esterified phosphonate group involving the provision of a compound having an esterified phosphonate group and contacting the compound with GS-7340 Ester Hydrolase

14. claims: 135-165, 199, 203, 207, 213, 217, 221, 225, 237

Prodrugs and method for identifying prodrugs having an esterified carboxyl group involving the provision of a compound having an esterified carboxyl group and contacting the compound with GS-7340 Ester Hydrolase.

15. claims: partly: 166-168, 170-195

Method for identifying prodrugs having an esterified phosphonate group involving the provision of a compound having an esterified phosphonate group and contacting the compound with an extract of peripheral blood mononuclear cells.

16. claims: 169, partly: 166-168, 170-195

Method for identifying prodrugs having an esterified carboxyl group involving the provision of a compound having an esterified carboxyl group and contacting the compound with an extract of peripheral blood mononuclear cells.

17. claims: partly 1,23,24,38-44

Methods for identifying a compound and determining the anti-HIV activity and susceptibility to hydrolysis of its phosphonate esters by GS-7340 Ester Hydrolase. Means for the method.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 21,22,28, 29,30,45, 196-213, partially 1,8,13-17,20,23,27

Claims 23 and 28 cannot be searched because the backreference is not clear; Art 6, PCT. Present claims 1,8,13-17,20,27 relate to an extremely large number of possible methods. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which relate to nucleoside derivatives and foscarnet derivatives.

At least one feature of claims 21,22,29,30,45 is directed to subject-matter of non-technical nature. Claims 29, 30, 45 inter alia include a method for doing business (Rule 39.1(iii) PCT)

Claims 196-213 cannot be searched because they belong to the group of "reach-through claims". Such claims lack clarity, support and sufficient disclosure according to the trilateral study project 3b- "Report on Comparative Study on Biotechnology Patent Practices".

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International Application No  
PCT/EP 03/12423

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0139724	A 07-06-2001	AU 1949701 A BR 0016058 A CA 2393410 A1 CN 1414854 T EP 1233770 A2 JP 2004500352 T WO 0139724 A2 US 2004019232 A1 US 2004127735 A1 ZA 200204194 A		12-06-2001 15-07-2003 07-06-2001 30-04-2003 28-08-2002 08-01-2004 07-06-2001 29-01-2004 01-07-2004 20-08-2003
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Information on patent family members

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Patent document cited in search report	Publication date		Patent family member(s)	Publication date
US 2004121316	A1	24-06-2004	WO 03090690 A2	06-11-2003
			WO 03091264 A2	06-11-2003
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